Determinants of the Fatigue Life of Musculoskeletal Tissues

Sean Gallagher, PhD, CPE
Auburn University

While the effects of physical risk factors on MSD development have been a primary focus of musculoskeletal disorder (MSD) research, it is clear that psychological stressors and certain personal characteristics (e.g., aging, sex, and obesity) are also associated with increased MSD risk. The psychological and personal characteristics listed above share a common characteristic: all are associated with disruption of the body's neuroendocrine and immune responses resulting in an impaired healing process. An impaired healing response may result in reduced fatigue life of musculoskeletal tissues due to a diminished ability to keep pace with accumulating damage (perhaps reparable under normal circumstances), and increased vulnerability of damaged tissue to further trauma owing to the prolonged healing process. Research in engineered self-healing materials suggests that decreased healing kinetics in the presence of mechanical loading can substantially reduce the fatigue life of materials. A model of factors influencing damage accrual and healing will be presented.

INTRODUCTION

Musculoskeletal disorders (MSDs) are comprised of a variety of inflammatory and degenerative conditions in musculoskeletal tissues, which may involve muscles, tendons, ligaments, and peripheral nerves. They are prevalent in society and result in substantial direct and indirect costs for both individuals and industry (Global Burden of Disease, 2018; Bevan, 2015; Hoy, et al., 2015) The association of physical work risk factors and MSDs has been well-studied (e.g., NIOSH, 1997; National Research Council – Institute of Medicine, 2001), and include factors such as high force demands, repetitive work, adoption of non-neutral postures, and/or exposure to vibration (Bongers, De Winter, Kompier, & Hildebrandt, 1993; Bongers, Kremer, & ter Laak, 2002; Deeney & O'Sullivan, 2009; Hauke, Flintrop, Brun, & Rugulies, 2011). Certain personal characteristics are consistently associated with the development of MSDs, including age, sex, and obesity (National Research Council – Institute of Medicine, 2001). MSDs are also associated with psychosocial stress at work, such as high psychological job demands and low job control (Deeney & O'Sullivan, 2009; Davis & Heaney, 2000).

FATIGUE LIFE

The fatigue life of a material (designated N_f) is defined as "the number of cycles of stress or strain of a specified character that a given specimen sustains before failure of a specified nature occurs." Such failure could be defined as the initiation of damage, damage reaching a specified size, or complete material failure, for example. In non-biological materials, fatigue life is solely dependent on two factors: the strength of the material and the load stress characteristics. However, biological tissues have an additional factor that influences fatigue life. This additional factor is the ability to repair tissues damaged due to exposure to repeated stress. Clearly, this repair capacity would be expected to extend the fatigue life of the tissue.

A common finding from in vitro or ex vivo material testing of musculoskeletal tissues is that the fatigue life of tissues in these conditions appear to be much lower than that necessary to maintain the health of the material throughout one's lifetime. For example, in vitro tests on the human extensor digitorum longus indicated that at a stress level of 20 MPa (20% of ultimate tensile strength), the fatigue life of these tendons in vitro was about 300,000 cycles. This is the equivalent of approximately four months of normal walking activity (Schechtman & Bader, 1997). Similar findings have been shown with other musculoskeletal materials (e.g., Thornton & Bailey, 2013; Shepherd & Screen, 2013; Carter & Hayes, 1976; Brinckmann, Biggemann, & Hilweg, 1988; Gallagher, et al., 2007). Clearly, there must be a reason for the considerable difference between the fatigue life obtained in vitro compared to that observed in life. It is probable that the extension in musculoskeletal tissue life is due to the healing and remodeling processes present in these biological tissues.

However, it is known that there are factors that can impair the effectiveness of the healing response. Such an impairment would be expected to have a deleterious effect on the fatigue life of a self-healing tissue.

IMPAIRMENT OF THE HEALING PROCESS

Psychological stress and healing

Psychological stress is known to negatively impact the healing of tissues through well-established mechanisms (Chrousos & Gold, 1992; Guo & DiPietro, 2010). This mechanism involves the secretion of various glucocorticoids and catecholamines (e.g., norepinephrine and epinephrine) that inhibit the healing response, as well as reducing sleep time and quality (also known to negatively impact healing), not to mention the development of certain unhealthy behaviors that can lead to additional mechanisms that reduce the effectiveness of healing (such as smoking and alcohol use) (Guo & DiPietro, 2010).

Psychological stress has been shown in many studies to have a significant impact in terms of inhibiting the healing response of tissues (Godbout & Glaser, 2006; Chrousos & Gold, 1992). This has been demonstrated in both animal and human studies. For example, one study found that students facing examination

stress during the academic year demonstrated a 40% increase in the time it took to heal a 3.5 mm biopsy punch wound on the hard palate compared to an identical wound placed on the contralateral side during a period of vacation (Marucha, Kiecolt-Glaser, & Favagehi, 1998). All 11 subjects demonstrated a slowed healing response under stress and averaged a 3-day increase in the time to heal. In other research, caregivers operating in stressful situations have demonstrated a similar response (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995). Compared with controls, stressed caregivers experienced wound healing averaging 9 days longer (48 versus 39 days). Similarly, individuals living in hostile marital relationships showed a 60% decrease in the rate of wound healing, which was associated with a decrease in IL-1beta, IL-6 and TNF-alpha levels at the wound site (Kiecolt-Glaser, et al., 2005).

A systematic review and meta-analysis examined psychological stress and wound healing in humans (Walburn, Vedhara, Hankins, Rixon, & Weinman, 2009). Of 22 studies accepted for inclusion in the review, 17 found that psychological stress was associated with impaired wound healing or dysregulation of biomarkers associated with wound healing across a variety of experimentally induced wounds and different conceptualizations of psychological stressors. Results of the meta-analysis (involving 12 studies) demonstrated a pooled effect size of r = -0.42 (95% CI = -0.51, -0.32), indicating that greater levels of psychological stress are associated with impaired wound healing.

Age

It is commonly recognized that individuals of increased age have a healing response that takes significantly longer than individuals of a younger age (Guo & DiPietro, 2010). However, while the healing process takes longer, in healthy aged individuals, the quality of healing is not necessarily impaired (Gosain & DiPietro, 2004). The extended wound healing time appears to be due in part to a delayed inflammatory response. For example, some of the altered wound healing activity in peripheral tissues includes changes in the inflammatory phase, such as, reduced vascular permeability, reduced macrophage infiltration and function, delayed T-cell infiltration, increased pro-inflammatory cytokine and chemokine production, and reduced growth factor production (Swift, Burns, Gray, & DiPietro, 2001). The proliferative and remodeling phases are also affected by age-related changes, including slower collagen deposition and decreased remodeling (Guo & DiPietro, 2010). At the end of the process, decreased wound strength will often result (Gosain & DiPietro, 2004).

Sex

The rate of collagen synthesis is a critical factor in the healing of musculoskeletal tissues. Research over the past two decades has demonstrated that a sex difference exists with respect to the rate of collagen synthesis between males and females, with decreased collagen synthesis in the latter (Kjaer, et al., 2009). Females have a lower rate of basal collagen synthesis compared to males, and also demonstrate a decreased collagen synthesis rate compared to males after exposure to exercise (Miller B., et al., 2006a; Miller B. , et al., 2006b). This decreased collagen synthesis rate has been linked with estrogen levels, as varying levels of estradiol (one of the three estrogen hormones produced by the body) have been associated with a diminished rate of collagen synthesis in females (Hansen, et al., 2008). These findings are supported by in vitro studies in which estradiol receptors have been identified in ligaments (Sciore, Frank, & Hart, 1998), and that estradiol itself can inhibit collagen synthesis in ligaments and tendons (Liu, et al., 1996; Yu, Panossian, Hatch, Liu, & Finerman, 2001).

Obesity

Health issues associated with obesity are numerous, and include increased risk of type II diabetes, heart disease, high blood pressure, stroke, sleep apnea, and respiratory problems (Guo & DiPietro, 2010). In addition to these health problems, obese individuals demonstrate an impaired wound healing capability, along with an increased number of complications during the wound healing process (Guo & DiPietro, 2010). Many of these problems stem from a decrease in blood perfusion and ischemia present in adipose tissue. The same tension that causes a wound to experience dehiscence (bursting open) may also contribute to reduced perfusion at the wound site, leading to decreased delivery of oxygen and reducing availability of biochemical compounds necessary to heal the wound (Anaya & Dellinger, 2006; Wilson & Clark, 2004).

Type II Diabetes is strongly associated with obesity and can substantially decrease healing kinetics (Brem & Tomic-Canic, 2007; Lin, et al., 2017). Hypoxia is often observed in diabetic wounds and can prolong the injury healing time of wounds by increasing the levels of oxygen radicals in diabetics (Guo & DiPietro, 2010). A decrease in the amount of angiogenesis is also commonly observed in diabetics (Brem & Tomic-Canic, 2007). The neuropathy attendant to diabetes probably also increases wound healing times (Guo & DiPietro, 2010). Tendinopathy, tendon ruptures, and impaired tendon healing are all more prevalent among those with diabetes (Maffulli, Longo, Maffulli, Khanna, & Denaro, 2011). High blood glucose levels appear to inhibit proliferation of tendon derived stem cells and increase the rate of cell apoptosis (Lin, et al., 2017). Thus, healing of tendons appears to be significantly delayed in a hyperglycemic environment (Lin, et al., 2017).

THE INTERACTION OF DAMAGE AND HEALING

The evidence presented above indicates that there are several mechanisms that may lead to an impaired healing response when exposed to psychological stress, aging, sex, and/or obesity. Certainly, combinations of these factors may have additive or multiplicative effects in this regard. The question that arises is, “What happens when a biological tissue (exposed to repeated loading and damage accrual) experiences

a decrease in healing kinetics?" Unfortunately, the relationship of damage accumulation to healing is exceedingly difficult to ascertain precisely in vivo. In a search of the literature, we found no research that assessed concurrent fatigue damage development and healing rates in musculoskeletal tissues. However, there is some data that may be relevant to this question from the field of engineered self-healing materials. These are materials that have been designed to mimic the healing process of biological materials and provide a method of repairing damage accumulated in the material due to fatigue failure. Such studies can provide some insight (clearly with caveats) into the benefits of having a self-healing process on material fatigue life, as well as how the degree of benefit can vary as the result of the rate at which healing occurs.

A fascinating study by Jones and colleagues (2007) provides data on the extension of fatigue life provided by three different rates of healing in a self-healing polymer material. When the material experienced damage (crack formation), microcapsules containing dicyclopentadiene (DCPD) would rupture and fill the crack. This compound was then acted upon by one of three catalyst treatments (each catalyst having different healing rates). The slowest healing treatment used the catalyst as received, the moderate healing condition used the catalyst but in recrystalized form, and the fastest healing process use the catalyst in a freeze-dried state. All specimens were loaded identically using a Kmax of 0676 MPa/m2, R=0.1 and a loading frequency of 5 Hz.

Results of this study demonstrated that the presence of a self-healing process significantly increased fatigue life of the material compared to the control condition (which had no healing capability), even when healing kinetics were relatively slow. Compared with the control condition, the condition with slow healing kinetics exhibited a fatigue life extension of approximately 17 times that of the control condition (1.5 million versus 86,000 cycles). The life extension multipliers of the moderate and fast healing kinetics conditions were 25 (2.2 million cycles) and 32 (2.8 million cycles) times the fatigue life of the control condition, respectively. These data suggest that the ability of a material to self-heal can confer impressive benefits in terms extending a material's fatigue life. However, these data also demonstrate that the degree to which the material fatigue life is extended is highly dependent on the rate of healing. In this example, the slowest healing process exhibited a fatigue life extension that was only 54% that of the fast-healing condition. Moderate healing kinetics demonstrated about 80% of the fatigue life extension compared to the fast-healing condition (Jones, Rule, Moore, Sottos, & White, 2007). Thus, a dose-response relationship was observed between the rate of healing and the degree to which fatigue life was extended in this self-healing material.

Implications

The fatigue life of musculoskeletal tissues may be primarily a function of three parameters: the strength of the material, the load to which it is exposed, and the rate at which damage can be healed. Changes in any of these parameters may have a significant impact on musculoskeletal health. In prior models of the effects of psychosocial stress, emphasis has generally been placed on the loading (damage development) side of the equation, but there are certainly indications that psychological stress may play an influential role in healing kinetics, and this may be a significant reason for the relationship observed between psychological stress and increased MSD prevalence and incidence. In fact, our sense from the literature is that the impact psychological stress has on healing might have a greater impact on the MSD development than the increases in loading that may accrue from such stress. However, it may well be that psychological stress has an influence on both damage accrual and impaired healing.

However, as discussed earlier, it is not just psychological stress that can negatively affect the healing process. Personal characteristics such as age, gender, and obesity are known to influence the healing process. Figure 1 provides a model of this relationship. In this model, we talk in terms of the kinetics of damage development and healing. If the damage kinetics are lower than the healing kinetics, this would be expected to lead to a restorative repair of the musculoskeletal tissue. However, if damage kinetics exceed the healing kinetics, damage will accumulate in the tissue and this accumulation will continue as long as repeated stress is experienced. Damage kinetics are primarily the result of repeated stress experienced by the tissues and the resultant process of fatigue failure. The higher the rate of cumulative damage, the greater the risk that damage may exceed the healing capacity. Healing kinetics can be positively influenced by factors such as good quality sleep and exercise. However, the focus of this article is that psychological stress, aging, obesity and certain disease states (such as diabetes) can negatively impact healing rates.

Obviously, lower rates of fatigue damage and a higher rates of healing kinetics are the most desirable condition and would lead to restorative repair of any damage incurred. However, all too often, the damage kinetics exceed the healing capacity, potentially leading to accumulating damage in the tissues and development of MSDs.

SUMMARY

Several lines of evidence indicate that, similar to other materials, musculoskeletal tissues subjected to repeated stress experience accumulating damage as the results of a fatigue failure process. However, unlike other materials these tissues have a healing process that can repair damage that may be incurred. This process surely extends the fatigue life of tissues. However, certain factors can impair the healing process, which would be expected to decrease the fatigue life of injured tissues. These factors include psychological stress, aging, sex, and obesity (all associated with increased MSD risk). These factors, through their effects on healing, could be considered modifiers of a fatigue failure process and the fatigue life of tissues. Some of these factors may have effects on not just impairment of healing but may also affect the loading side of the equation.

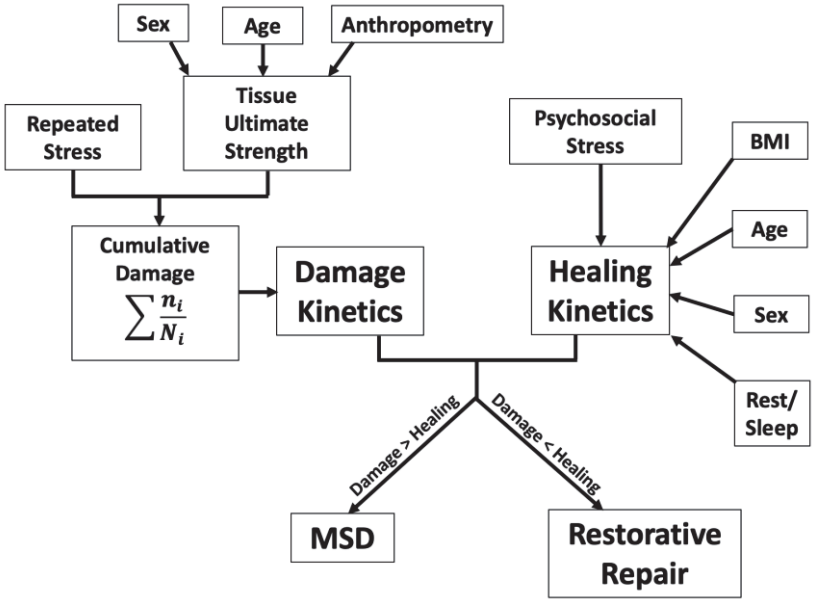

Figure 1. A model of the interaction of damage and healing kinetics on musculoskeletal health.

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